UCP2 regulates energy metabolism and differentiation potential of human pluripotent stem cells.

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Public Summary:
It has been assumed, based largely on morphologic evidence, that human pluripotent stem cells (hPSCs) contain underdeveloped, bioenergetically inactive mitochondria. In contrast, differentiated cells harbour a branched mitochondrial network with oxidative phosphorylation as the main energy source. A role for mitochondria in hPSC bioenergetics and in cell differentiation therefore remains uncertain. Here, we show that hPSCs have functional respiratory complexes that are able to consume O(2) at maximal capacity. Despite this, ATP generation in hPSCs is mainly by glycolysis and ATP is consumed by the F(1)F(0) ATP synthase to partially maintain hPSC mitochondrial membrane potential and cell viability. Uncoupling protein 2 (UCP2) plays a regulating role in hPSC energy metabolism by preventing mitochondrial glucose oxidation and facilitating glycolysis via a substrate shunting mechanism. With early differentiation, hPSC proliferation slows, energy metabolism decreases, and UCP2 is repressed, resulting in decreased glycolysis and maintained or increased mitochondrial glucose oxidation. Ectopic UCP2 expression perturbs this metabolic transition and impairs hPSC differentiation. Overall, hPSCs contain active mitochondria and require UCP2 repression for full differentiation potential.

Scientific Abstract:
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